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Antagonists of monocyte chemoattractant protein 1 identified by modification of functionally critical NH₂-terminal residues.

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Monocyte chemoattractant protein (MCP)-1 analogues were designed to determine the role of the NH₂-terminal region in structure and function. The NH₂-terminal residue was important for function and receptor binding, as it could not be deleted or extended. However the NH₂-terminal pyroglutamate residue of the wild type was not essential as it could be replaced by several other noncyclic amino acids without loss of activity. Residues 7-10 were essential for receptor desensitization, but were not sufficient for function, and the integrity of residues 1-6 were required for functional activity. A peptide corresponding to MCP-1, 1-10 lacked detectable receptor-binding activities, indicating that residues 1-10 are essential for MCP-1 function, but that other residues are also involved. Several truncated analogues, including 8-76, 9-76, and 10-76, desensitized MCP-1-induced Ca²⁺ induction, but were not significantly active. These analogues were antagonists of MCP-1 activity with the most potent being the 9-76 analogue (IC₅₀ = 20 nM). The 9-76 specifically bound to MCP-1 receptors with a K_d of 8.3 nM, which was three-fold higher than MCP-1 (K_d 2.8 nM). The 9-76 analogue desensitized the Ca²⁺ response to MCP-1 and MCP-3, but not to other CC chemokines, suggesting that it is MCP receptor specific. The availability of these compounds will be helpful in evaluating MCP receptor antagonists as anti-inflammatory therapeutics.

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